

Office Action Summary	Application No.	Applicant(s)
	10/582,637	MICHELSEN ET AL.
	Examiner	Art Unit
	CYNTHIA B. WILDER	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 29 July 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-5 and 9-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-5 and 9-18 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

SUPPLEMENTAL FINAL ACTION

1. The previous Office action mailed 9/9/2008 is vacated in lieu of this Supplemental Final Office action. The previous Final Office action was inadvertently mailed to Applicant in error. This Office action is being submitted to address the claims 1-5 and 9-18. Claims 1-5 have been amended. Claims 6-8 have been canceled. Claims 9-18 have been added. Claims 1-5 and 9-18 are pending and addressed in this Office action. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new ground(s) of rejection necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Accordingly, all rejections maintained in this Office action do not contain those sections of Title 35 U.S. Code as these sections can be found in the prior Office action filed 4/30/2008.

Previous Rejections

3. The objections to the specification are maintained and discussed below. The claim rejections under 35 USC 112 second paragraph are withdrawn in view of Applicant's amendment of the claims. The prior art rejections under 35 USC 102(b) are maintained and discussed below. The prior art rejections under 35 USC 103(a) are maintained and discussed below.

Specification

4. Once again, the use of the trademarks "Tween", "Triton" at page 6 and 8, "MagPrep" at pages 8-10, "PicoGreen" and Ribopage at page 9 have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Response to Arguments

5. Applicant traverses the rejection on the grounds that the specification provides a detailed description of the various reagents and or applications recited in the instant specification. Applicant states that a quick search on PUBMED can verify the meanings conveyed by those terms is generically understood in the field of molecular biology.

All of the arguments have been thoroughly reviewed and considered but are not found persuasive because MPEP states that the trademark should be "capitalized" and accompanied by the generic terminology wherever it appears. The specification does not meet these requirements. Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 102

6. Once again, claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Gundling (20020068821, June 2002). Regarding claim 1, Gundling teaches a method for the isolation of RNA from the sample, the method comprising providing a metal oxide support material (0012), wherein said metal oxide support material is a magnetite (F_3O_4) (Table 1, 0030) providing a binding buffer which comprises guanidinium thiocyanate in a concentration of between 2M and 10M, more preferably between 3M and 6M, mixing the sample with the metal oxide support material and the binding buffer, where a phosphate concentration which supports the binding of RNA is present in this mixture and isolation of the solid phase with the bound RNA (see Examples 1 and 2).

Regarding claim 2, Gundling teaches wherein the solid phase is optionally washed and the RNA is subsequently eluted from the solid phase (0018).

Regarding claim 3, Gundling teaches wherein the elution is carried out using an elution buffer which facilitates a pH range between 7 and 9 and comprises phosphate (0018).

Therefore, Gundling meets the limitations of the claims recited above.

Response to Arguments

7. Applicant traverses the rejection on the following grounds: Applicant states the cited prior art, Gundling does not teach the utilization of a binding buffer comprising phosphate. Applicant states that the reference does not disclose a binding buffer containing phosphate and additionally, the RNA samples used in example 1 and 2 seem to be non-natural samples so there should not be any phosphate present. Applicant states that Gundling only teaches phosphate-containing buffers using as elution buffers. Applicant states that Gundling is silent with the presence of phosphate having any effect on the binding properties of RNA and thus does not teach the preferential RNA binding as claimed herein. Applicant states that Gundling does not teach or suggest methods for discriminating RNA versus DNA and/or that the reagents could be optimized for the isolation of RNA molecules.

8. All of the arguments have been thoroughly reviewed and considered but are not found persuasive. In response to Applicant's arguments that Gundling does not teach the utilization of a binding buffer comprising phosphate, the Examiner respectfully disagree as Gundling specifically teaches at page 2, paragraph 0013 the following:

"["B]inding buffers" facilitate binding of nucleic acid present in a test sample to metal oxide support materials. It has been found that nucleic acid will bind to metal oxide support materials in an extensive variety of buffers without regard to the pH of the buffer. Hence, the binding buffer can have an acidic pH (less than 7), neutral pH (equal to 7), or a basic pH (greater than 7). Binding buffers will generally comprise a buffering system. Buffering systems are well known and a matter of choice for those skilled in the art. Buffering systems are typically an

aqueous solution of a weak acid and its corresponding base, such as, for example, sodium phosphate and phosphoric acid."

Accordingly, this argument is not found persuasive.

In response to Applicant's arguments concerning the inoperability of the method as recited in the Examples 1 and 2, the Examiner asserts that the arguments appear to be based on Applicant's opinion without any factual evidence to support the assertion. MPEP states "objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). Further, it is noted that the instant claims to not require any specific type of samples, thus the teachings of a "non-natural sample" as implied by Applicant would fall within the scope of the claims.

In responds to Applicant's arguments concerning the preferential isolation of RNA, it is noted that contrary to Applicant's arguments, Gundling teaches that the method is capable of separating or isolating DNA and RNA (0010) and further depicts in the Example wherein RNA is separately extracted and eluted from the samples (see Examples beginning at page 3). Thus, the selectivity of the phosphate to target binding of RNA to the solid phase is an inherent property of the phosphate in the binding buffer taught by Gundling. MPEP states that "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."

Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >*In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004)." Thus, this argument is not found persuasive. Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 103

9. Once again, claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gundling as previously applied above in view of Madden et al (20050054847, effective filing date August 2003). Regarding claim 4, Gundling et al teach a method and kit for the isolation of RNA from samples wherein the method comprising providing a magnetite solid phase; providing a binding buffer which comprises guanidinium thiocyanate, mixing the sample with the magnetite solid phase and the binding buffer, where a phosphate concentration which supports the binding of RNA is present in the mixture, isolation of the solid phase with the bound RNA and further eluting the RNA from the solid phase.

Gundling do not expressly teach wherein the binding buffer comprises a chelator, such as EDTA in a concentration of between 5 and 200 mMol.

Madden et al teach method and kit for purification of RNA. Madden et al teach an RNA binding buffer which is preferably used in the purification of RNA, said binding buffer comprising from 1 to 9M guanidine isothiocyanate and 25 mM EDTA or another chelating agent, like EDTA (0034 and 0238).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the claimed invention to incorporate a chelating agent, such as EDTA into the RNA isolation method and kit of Gundling, since the combination of the EDTA with the binding buffer of Gundling does not alter the effects of the binding buffer and could be used to predictably achieve the results of purifying RNA in an efficient manner as suggested by Madden.

10. Once again, claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gundling as previously applied above in view of Kilaas et al (WO 2004/003231, filing date July 2003). Regarding claim 5, Gundling teaches a method for isolating RNA as previously described above, wherein a magnetite solid phase is used in the assay. Gundling do not expressly teach the diameter and specific surface area of the magnetite particles.

Kilaas et al provides a general teaching of magnetic particles for binding a target substance, wherein the target substance is DNA or RNA (page 1 and 10). Kilaas et al teach wherein the magnetic particle has a diameter of 0.1 μ m to 100 μ m (page 10). Kilaas et al do not expressly teach the specific surface area. However, MPEP states that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, this is particularly true as the specification does not provide any evidence of unexpected results using the claimed specific surface area of the magnetite particles.

Response to Arguments

11. Applicant traverses the rejection on the grounds that the failure of primary Gundling reference to teach each and every element of Applicant's claimed invention because the reference is silent regarding the use of phosphate based binding buffers and the selectivity of the reagents in isolating RNA molecules. Applicant states that there is nothing in Madden about the isolation of RNA and or methods for selective isolation of RNA in the presence of DNA or the usefulness of such reagents in selective isolation of RNA molecule from a mixed pool of nucleic acids.

Applicant states that with regards to the Kilaas reference, it provides further details about magnetic particles, but does not offer any hits as to the unexpected utility thereof in the selective isolation of RNA in the presence of DNA.

12. All of the arguments have been thoroughly reviewed and considered but are not found persuasive as the Examiner maintains that the primary reference of Gundling teaches the presence of phosphate in the binding buffer (see above and Gundling at paragraph 0013). Thus, this argument is deemed moot.

In regards to Applicant's arguments concerning the selective isolation of RNA, the Examiner maintains that the primary reference of Gundling meets this limitation as it teaches the selective elution of RNA from the solid phase (see Example 2). Additionally, it is further noted that the features upon which applicant relies (i.e., *selective isolating of RNA in the presence of DNA* is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26

USPQ2d 1057 (Fed. Cir. 1993).

In regards to Applicant's arguments concerning the secondary references of Madden et al (claims 4) and Kilaas (claim 5), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the secondary reference of Madden et al teaches the use of EDTA in the binding buffer for the purification of RNA (see 0034 and 0238). As noted in the prior Office action, the use of a chelating agent in the binding buffer for RNA does not effect the function of the binding buffer and can be used to predictably achieve the results of purifying RNA in an efficient manner as suggested by Madden. The secondary reference of Madden provides sufficient motivation for one of ordinary skill in the art to incorporate the element into the binding buffer of Gundling.

With regards to the teaching of Kilaas, the secondary reference provides sufficient motivation for one of ordinary skill in the art to utilize the magnetic particles having the properties described therein. Accordingly, Applicant's arguments are not sufficient to overcome the prior art rejections. These rejections are maintained.

New Grounds of Rejections

THE NEW GROUNDS OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim interpretation

The claims 10, 17 and 18 recite "wherein the RNA molecule is selectively isolated compared to DNA molecule". The term "selectively isolated" is extremely broad and it cannot be determine how the limitation defines or distinguishes the claim over the prior art. Neither the specification nor claims provide a limiting definition of the term "selectively" as it relates to the isolation of RNA as compared to DNA. Thus, for the purpose of application of prior, the term is being interpreted by the Examiner as extraction or purification or isolation of RNA.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-5 and 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gundling as previously applied above in view of Belly et al (US 7, 267,950 and further in view of Goudsmit et al (2001/0021518, September 2001).

Regarding claim 1, 10, 12, 17 and 18, Gundling et al teach a method the isolation of RNA from samples comprising a mixture of nucleic acids wherein the method comprises providing a magnetite solid phase; providing a binding buffer which comprises guanidinium thiocyanate at a concentration of greater than 3 mol/l (entire patent and 0022), mixing the sample with the magnetite solid phase and the binding buffer, where a phosphate concentration which supports the binding of RNA is present in the mixture, isolation of the solid phase with the bound RNA and further eluting the RNA from the solid phase (Example 1 and 2). Gundling further teaches wherein the binding buffer may comprise sodium phosphate based on the investigator's desired pH of the buffer solution (0013).

Belly et al supports this assertion made by Gundling. Belly et al provides a general method of extracting RNA from biological systems comprising a mixture of nucleic acids, wherein the RNA extraction method comprises the use of a lysis/binding buffer comprising a guanidinium salt 4 M or greater and 100 mM sodium phosphate (col. 3, 46-67). Belly et al teach wherein the RNA extraction method additionally comprises, wash buffers I and II, elution buffer and silica gel membrane (col. 3-4). Belly et al teach that in the presence of the binding buffer, nucleic acids adsorb to the silica gel (col. 4)

Gundling in view of Belly do not expressly teach wherein the binding buffer comprises a chelator, such as EDTA in a concentration of between 5 and 200 mMol.

Goudsmit et al teach a method of isolating single stranded nucleic acid material (RNA) from double stranded nucleic acid material, said method comprising: contacting a mixture of both single stranded and double stranded nucleic acid with a binding buffer comprising a chaotropic agent in a concentration of between 1-10 M, a chelating agent, EDTA in a concentrating greater than 10 mM and preferably not higher than 1 M; mixing the sample with a silica based particle such as SiO_2 crystals and other forms of silicon oxide (0007-0012). Goudsmit et al teach the particle have a size of from about 0.05 to 500 μm (0012).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the claimed invention to incorporate a chelating agent, such as EDTA into the RNA isolation method and kit of Gundling in view of Belly et al, since the combination of the EDTA with the binding buffer of Gundling does not alter the effects of the binding buffer but rather aid in selectively isolating RNA from a mixture of nucleic acid as suggested by Goudsmit et al. The ordinary artisan could predictably achieve the results of purifying RNA in an efficient manner as suggested by Goudsmit for subsequent analysis such as by amplification.

Regarding claim 2, Gundling teaches wherein the solid phase is optionally washed and the RNA is subsequently eluted from the solid phase (0018).
Regarding claim 3, Gundling teaches wherein the elution is carried out using an elution buffer which facilitates a pH range between 7 and 9 and comprises phosphate (0018).

MPEP states “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding claims 4 and 9, Goudsmit et al teach wherein the binding buffer comprises a chelator, wherein the chelator is EDTA in a concentration of at least 10 mM but not greater than 1 M (0008). MPEP states “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding claim 5, Goudsmit et al teach the solid phase may be silicon -based material, such as SiO₂ crystals and other forms of silicon oxides having a particle size of from about 0.05 to 500 μm (0012). MPEP states “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding claim 11, Gundling et al teach a method comprising at least a magnetite solid phase and a binding buffer having a GTC concentration of greater than 3 mol/l (entire patent and 0022). Goudsmit et al also teach wherein the buffer comprises GTC at a concentration of between 1-10 M (0008). MPEP states “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Regarding claim 13, Gundling et al teach wherein the method comprises one or more of the following: an elution buffer, a wash buffer or a phosphate salt solution (entire patent and 0022).

Regarding claim 14-16, Gundling et al teach wherein sodium phosphate may be added to the binding buffer to adjust the pH of the buffer as desired by the Investigator. Belly et al supports this assertion made by Gundling. Belly et al provides a general method of extracting RNA from biological systems wherein the RNA extraction method comprises the use of a lysis/binding buffer comprising a guanidinium salt 4 M or greater and 100 mM sodium phosphate (col. 3, 46-67). With regards to the limitations recited in the claims 15-16, these claims recite conventional nucleic acid manipulation reagents and methodologies, as well as well as routine optimization or reaction components, concentrations, and parameters. Routine optimization is not considered inventive and no evidence has been presented that the selection of specific reagents used for the same purpose and concentrations were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Further, MPEP states that “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, one of ordinary skill in the art would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations an/or expanded

applications. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods.

Conclusion

15. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GARY BENZION/
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